REMARKS

Claims 1-16 are pending in this application. Claims 1-16 were rejected under 35 U.S.C. § 112, first paragraph.

By this amendment, claims 5, 7, 8, 13, 15 and 16 have been canceled, claims 1 and 9 have been amended and new claims 23-26 have been added without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments to claims 1 and 9 can be found, *inter alia*, throughout the specification including, for example, at page 10, line 19. Support for the new claims 23-26 can be found, *inter alia*, throughout the specification including, for example, at page 24, line 23, to page 25, line 2.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-16 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

The Examiner states that "the art teaches that the operability of any given ISS in one species of mammal is not a predictor of operability in any other mammalian species" and "[a]s the art indicates that the vast majority of these sequences would be inoperable in any given species, determining that the invention is inoperable in any given species would require undue

experimentation." Office Action, paragraph bridging pages 3-4. Although Applicants respectfully disagree with the Examiner's assessment of the state of the art with regard to operability of ISS in mammalian species[1], the pending claims are herein amended to administration of an ISS-containing polynucleotide to a single mammalian species, a human individual.

Applicants respectfully submit that immunostimulatory sequences operable in humans are described in the specification and are well-known in the art.[2] Applicants also agree with the Examiner that determining if any single ISS is operable in a given mammal, such as a human, would not require undue experimentation.

The Examiner further asserts that the disclosure does not "set forth teaching requirements unique to the use of CpG oligonucleotides in mammalian species outside of dogs and rabbits." Office Action, page 9. Applicants respectfully disagree with this assertion.

The specification provides adequate guidance to enable one of skill in the art to make and use the claimed invention, i.e., a method of delaying development of a symptom of papillomavirus infection in a human and a method of reducing severity of a papillomavirus infection in a human. Examples of ISS-containing polynucleotides for use in the claimed methods and methods for their synthesis are provided, for example, on pages 21-29. Examples of administration regimens are provided, for example, on pages 34-35. Examples of formulations are provided, for example, on page 36. Examples of dosage ranges of ISS-containing polynucleotides for use in the claimed methods are provided, for example, on page 37. Examples of means of administration are provided, for example, on pages 37-39. Means for assessment of palliation and/or improvement of one or more symptoms of papillomavirus infection are provided, for example, on pages 39-40. Such extensive disclosure provides

---

[1] Polynucleotides with immunostimulatory sequences active in cells of many mammalian species have been described in scientific literature, including human, monkeys, chimpanzees, cows, swine, dogs, cats, rabbits, mice and rats.

[2] See, for example, many of the references submitted January 29, 2002.

adequate guidance such that a skilled artisan would be able to practice the claimed invention without undue experimentation.

Applicants respectfully submit that the examples of papillomavirus infection treatment in the dog and rabbit animal models presented in the specification are sufficient to provide enablement for the claimed methods. As Applicants noted in a response to an Office Action filed July 3, 2002, MPEP §2164.02 states that an "*in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention" and that ""[c]orrelation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." The same section of MPEP also states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." It is well known in the art, and described in the specification, for example, on page 13, that a wide variety of animals are subject to papillomavirus infection. Rabbit and canine models used in this application are art-accepted models for the study of papillomavirus infection.[3] The Examiner has not provided any evidence that the animal models do not correlate with the claimed invention. Therefore, Applicants traverse the contention that enablement in these animal models is insufficient to enable the invention as claimed.

In the rejection, the Examiner states that the teachings of the cited reference Hartmann et al. "indicate that only the phosphorothioate oligonucleotides taught in the present disclosure would be useful in the methods of the present invention." Office Action, page 9. Applicants respectfully disagree.

Although Hartmann states that "[t]o have in vivo clinical utility, ODN must be administered is a form that protects them against nuclease degradation", Hartmann does not state that phosphorothioate oligonucleotides are the only form to accomplish this. In fact, Hartmann

---

[3] See, for example, Sundaram et al. (1998) and Schlegel et al. (U.S. Pat. No. 5,874,089), of record.

reports immunostimulatory activity of phosphodiester oligonucleotides in the paragraph bridging pages 1617 and 1618 and in the first full paragraph of page 1618. In the other reference cited by the Examiner in the Office Action, Agrawal states that the "overall immunostimulatory affects of phosphodiester and phosphorothioate CpG DNA are similar." Agrawal, page 115. Thus, Applicants respectfully submit that a phosphorothioate oligonucleotide is not the only useful polynucleotide for the claimed methods.

Lastly, with regard to claims 9-16, the Examiner has reiterated that the specification lacks enablement for a method "wherein the composition is administered prior to the development of a lesion or outside of the affected area" and contends that "antigen must be present at the time and in the proximity of the administered ISS." In the response to the Office Action filed March 7, 2003, Applicants present arguments which disagree with this contention. In the pending Office Action, the Examiner requests that Applicants expand the arguments "to indicate why it is not logical to expect that some source of antigen is required or why it is not reasonable to expect that the infection is the source of the requisite antigen." Office Action, pages 5 and 6.

Applicants respectfully maintain that, although claim 9 is directed to a method of reducing severity of a symptom of a papillomavirus infection in a mammal infected with a papillomavirus, in the claimed invention, an ISS-containing polynucleotide may be administered alone, without administration of a papillomavirus antigen.

Applicants' declaration, provided herewith[4], states that "ISS treatment induces regression of a papilloma lesion whether the ISS is administered at the site of the lesion (locally) or at a site distant from the lesion (systemically)." Van Nest Declaration, paragraph 3. Dr. Van Nest's declaration provides experimental results demonstrating that both local and systemic administration of ISS-containing polynucleotide leads to regression of papilloma lesions.

---

[4] Applicants herewith submit an unsigned declaration from Gary Van Nest, Ph.D. and will shortly submit a signed copy of the declaration. Thus, Applicants' respectfully submit that this response and amendment is responsive to the outstanding Office Action.

Without being held to any particular theory for the mechanism of the claimed invention, it is well known in the art that ISS-containing polynucleotides are effective in stimulating aspects of the immune system separate from acting as an antigen adjuvant. For example, ISS-containing polynucleotides are known to stimulate a non-antigen-specific, innate immune activity such as stimulation of NK cell activity, IFN-γ and/or IL-12 production. See, for example, Krieg (1996) *J. Lab. Clin. Med.* 128:128-133 and Krieg (2000) *Curr. Opin. Immunol.* 12:35-43, submitted herewith. Thus, ISS-containing polynucleotides have immunostimulatory activity outside of the presence of antigen and thus, an antigen source is not required for immunostimulatory activity.

In the previous Office Action, the Examiner cited Weiner et al. (IDS # 127), a reference in which the adjuvant activity of immunostimulatory oligonucleotides administered with antigen is evaluated. The Examiner states the "the prior art provides no working examples of those embodiments of the invention wherein the CpG oligonucleotide is administered away from a source of antigen." Office Action, mailed September 24, 2002, pages 6-7.

Applicants respectfully submit that examples of administration of ISS without the presence of antigen resulting in a response to an infection are known in the art. For example, Krieg et al. (1998, *J. Immunol.* 161:2428-2434, reference 77 submitted January 29, 2002, "Krieg") reports relatively long-lived resistance to the intracellular bacteria *Listeria monocytogenes* with administration of CpG DNA prior to infection challenge. Krieg states that the data "demonstrate that CpG DNA activates the innate immune response and heightens the resistance of mice to *L. monocytogenes* infection." Krieg, p. 2429, left column. Elkins et al. (1999, *J. Immunol.* 162:2291-2298, reference 54 submitted January 29, 2002) also reports that administration of CpG-containing oligonucleotides without antigen confers protection against lethal intracellular bacterial infection with *L. monocytogenes* and with *Francisella tularensis*. In this study, protection is optimal when the immunostimulatory oligonucleotides were administered several days before the bacterial challenge, thus the administration was in the absence of bacterial antigen.

Also, in the commonly-owned pending application, US 09/802,518 by Van Nest (filed March 9, 2001 and published as WO 01/068103 (reference 7 submitted October 18, 2002)), Van Nest exemplifies treating a symptom of herpes infection with administration of ISS-containing polynucleotides locally and systemically, without administration of herpes antigen. Van Nest exemplifies systemic administration of the ISS-containing polynucleotides through intraperitoneal injection in Example 2, page 37, line 17, through page 38, line 5, in WO 01/068103. At page 37, lines 17-31, Van Nest describes ISS therapy that is administered through injections. In the prosecution of US 09/802,518, Dr. Van Nest's Declaration states that in this referenced procedure "the ISS therapy referred to as "ISS injections" was administration of ISS-containing polynucleotides though intraperitoneal injections." Van Nest Declaration, paragraph 3, submitted in US 09/802,518, March 24, 2003.

In the claimed methods of the invention, ISS-containing polynucleotides are administered without papillomavirus antigen to a human individual. Applicants have demonstrated that ISS administered systemically and locally leads to reduction in severity and delay in development of a papillomavirus symptom (*e.g.*, a papilloma lesion). Applicants respectfully submit that the specification enables the claimed invention to one of skill in the art. In addition, examples known in the art support scenarios in which immunostimulatory oligonucleotides can effect a protective immune response in the absence of antigen.

In sum, the pending claims are in compliance with the enablement requirements.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001300.

Respectfully submitted,

Dated: August 7, 2003

By: Karen R Zachow

Karen R. Zachow
Registration No. 46,332

Morrison & Foerster LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5191
Facsimile: (858) 720-5125